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Person signing the certificate:
Jay Akhave
Signature Jay R Akhave *Date* 9.14.04

13 September, 2004

Commissioner for Patents
P O Box 1450
Alexandria
VA 22313-1450

Sub: Certified Foreign Priority Document on U.S. Application 10/688,606

Dear Sir:

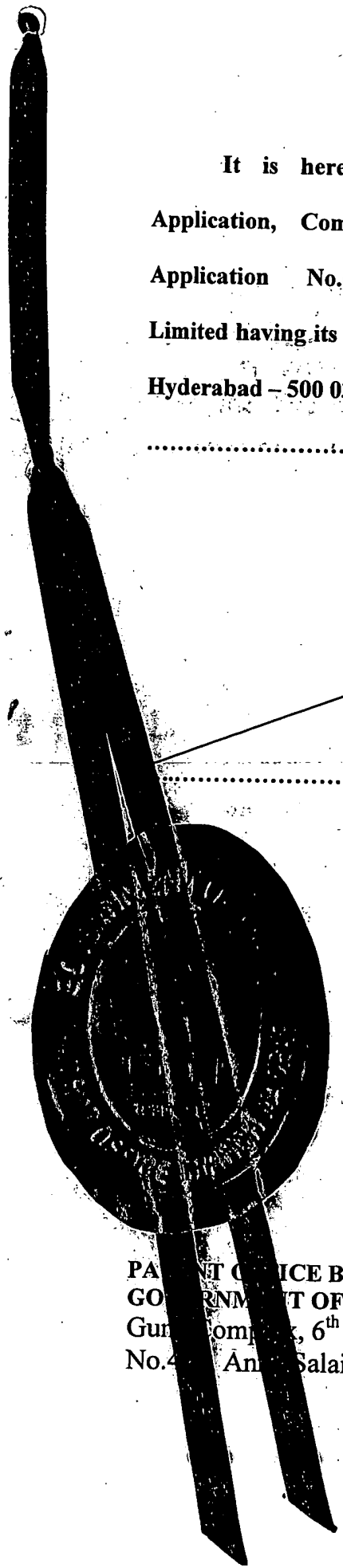
This is a submission of certified priority documents for the following U.S. Patent application.

U S Patent Application No.	10/688,606
Filing Date	10/17/2003
Title	Process for preparing Cefepime
First named Inventor	Vijay Kumar Handa
Art Unit	1624
Attorney Docket No.	2003-018
Filing Status	Filed awaiting First office Action

Sincerely,
Jay R Akhave

Jay Akhave
845 Pomello Dr
Claremont CA 91711
909 625 3492
US Patent Agent No 50,016

Encl: Certified Copy of Indian Application No. 669/CHE/2003



THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application, Complete Specification & Abstract of the extract of Patent Application No.669/CHE/2003, dated 21/08/2003 by M/s. Aurobindo Pharma Limited having its registered office at Plot No.2, Maitrivihar Complex, Ameerpet, Hyderabad – 500 038, Andhra Pradesh, India.

.....

.....In witness thereof

I have hereunto set my hand

Dated this the 4th day of August 2004

M. S. V

(M.S. VENKATARAMAN)
Assistant Controller of Patents & Designs

PA[illegible]NT O[illegible]ICE BRANCH
GO[illegible]RNM[illegible]T OF INDIA
Gu[illegible]om[illegible]x, 6th Floor, Annex.II
No.4[illegible] An[illegible]Salai, Teynampet,Chennai – 600 018

CERTIFIED COPY OF PRIORITY DOCUMENT

Received Rs 3000/- In Cash
Cheque/DD/PO/D Dt on 21/08/03
Vide C.B. No. 6427

FORM 1

THE PATENTS ACT, 1970

(39 of 1970)

APPLICATION FOR GRANT OF A PATENT OFFICE

[See section 5(2), 7/54 and 135]

We,

AUROBINDO PHARMA LIMITED
PLOT NO. 2, MAITRIVIHAR COMPLEX (Regd. Office)
AMEERPET
HYDERABAD – 500 038.

669/CHE/2003 (AN INDIAN ORGANIZATION)

21/8/2003

2. Hereby declare:-

(a) That we are in possession of an invention titled:-

(b) "**A PROCESS TO PREPARE CEFEPIME**"

(c) That the ~~Provisional~~/Complete Specification relating to this invention is filed with this application.

(d) That there is no lawful ground of objection to grant of a Patent to me/us.

21 AUG 2003

3. Further declare that the inventor(s) for the said invention is:-

(a) **VIJAY KUMAR HANDA**

(b) **ANAND G. KAMAT**

(c) **MEENAKSHISUNDERAM SIVAKUMARAN**

ORIGINAL

C/o. AUROBINDO PHARMA LIMITED
PLOT NO. 2, MAITRIVIHAR COMPLEX (Regd. Office)
AMEERPET
HYDERABAD – 500 038.

(a) to (c) : **CITIZENS OF INDIA**

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows:-

(a) NIL

(b) NONE

5. We state that the said invention is an improvement in or modification of the particulars of which are as follows and of which we are the Applicant/Patentee:

(a) NIL

(b) NONE

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application be deemed to have been filed on .... under section 16 of the Act:

NONE

7. That we are the assignee or legal representative of the true and first Inventors.

8. That our addresses for service in India is as follows:

Head Office

AUROBINDO PHARMA LIMITED
Plot No. 2, Maitrivihar Complex,
Ameerpet,
Hyderabad - 500 038 (A.P).

Phone No. : 91-40-23741083
Fax No. : 91-40-23741080; 23740591

9. Following declaration was given by the inventor(s) or applicant(s) in the convention country:-

NONE

We the true and first inventors for the invention or the applicant(s) in the convention country declare that the applicant(s) herein are our assignee or legal representative:

(a) **VIJAY KUMAR HANDA** Vijay Kumar Handa

(b) **ANAND G. KAMAT**

(c) **MEENAKSHISUNDERAM SIVAKUMARAN**

10. That to the best of my/our knowledge, information and belief the fact and matters stated herein are correct ad that there is no lawful ground of objection to the grant of patent to me/us on this application.

11. Following are the attachments with the application:-

(a) Complete Specification (3 copies).

(b) Drawings (3 copies).

(c) Priority document(s)

(d) Statement and undertaking on Form 4..... None.

(e) Power of Attorney

(f) Form 3

(g) Form 19

(h) Fee Rs.5,000/- in Bank Draft bearing No. 020139
Dated 8/8/03 on State Bank of Hyderabad.

We request that a Patent may be granted to us for the said invention.

Dated this 18th day of August, 2003.

.....
(Dr. M. SIVAKUMARAN)
DIRECTOR

ARABINDO PHARMA LTD. INDIA

TO
THE CONTROLLER OF PATENTS,
THE PATENT OFFICE,
~~**CALCUTTA/NEW DELHI/MUMBAI/CHENNAI**~~
CHENNAI

Form-2

THE PATENT ACT, 1970

COMPLETE

SPECIFICATION

(SECTION 10)

TITLE

"A PROCESS TO PREPARE CEFEPIME"

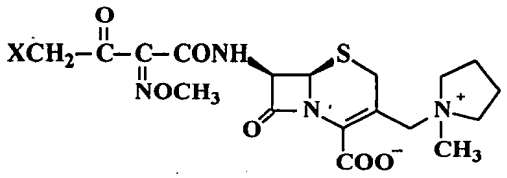
APPLICANT

AUROBINDO PHARMA LIMITED
HAVING REGISTERED OFFICE AT
PLOT NO. 2, MAITRI VIHAR COMPLEX,
AMEERPET, HYDERABAD – 500 038,
ANDHRA PRADESH, INDIA,
AN INDIAN ORGANIZATION

The following specification particularly describes and ascertains the nature of this invention and the manner in which the same is to be performed.

FIELD OF THE INVENTION

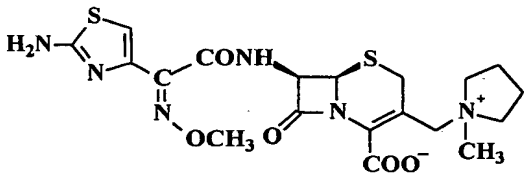
The present invention relates to a process for the preparation of Cefepime by using novel intermediates of the general Formula,



where X represents Bromine or Chlorine atom

BACKGROUND OF THE INVENTION

Cefepime, also known as 7-[(*Z*)-2-(2-Amino-4-thiazolyl)-2-(methoxyimino)acetamido]-3-[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate is a useful broad spectrum antibiotic cephalosporin and has the chemical structure of Formula I

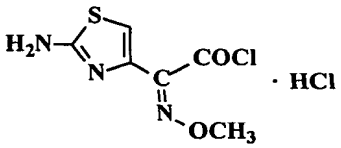


Formula I

Cefepime and its preparation has been first disclosed in US Patent 4,406,899. Two reaction schemes have been discussed in this patent to prepare Cefepime. Both of these schemes make use of the protecting groups that require additional blocking and deblocking steps. Furthermore, the exemplified process makes use of a chromatographic purification to obtain Cefepime zwitterion.

US Patent 4,754,031 describes a process where 2-(2-amino-4-thiazolyl)-2-methoxyiminoacetic acid is activated by reacting with methanesulfonyl chloride to form an anhydride for acylation of 7-Amino-3-[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate to obtain Cefepime. Although this process does not use protecting groups but it requires column chromatography as a purification method which is not practical in manufacturing.

US Patent 5,594,129 describes preparation of Cefepime wherein acid chloride hydrochloride of the Formula,



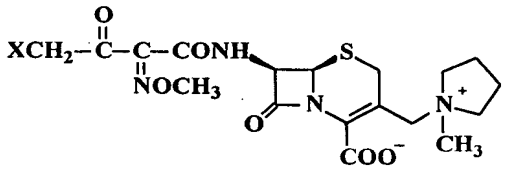
has been used for the *N*-acylation of 7-Amino-3-[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate under anhydrous conditions. The use of the same acid chloride hydrochloride in aqueous conditions for *N*-acylation to prepare Cefepime has been

demonstrated in the US Patent 5,594,130. In both of these US patents, the preparation of the desired acid chloride hydrochloride involves first the conversion of *syn*-2-(2-amino-4-thiazolyl)-2-methoxyiminoacetic acid to the corresponding hydrochloride salt which is then treated with chlorinating agent under specifically defined reaction conditions to obtain the *syn-isomer* of 2-(2-amino-4-thiazolyl)-2-methoxyiminoacetyl chloride hydrochloride that contains less than about 5% of the undesirable anti-isomer which may affect the subsequent acylation reaction to obtain the antibiotic.

Cephalosporins have been prepared in literature through an alternate method in which the amino group in the cephem nucleus is first acylated with 4-halo-2-methoxyimino-3-oxobutyric acid and the thiazolyl ring formation is subsequently effected with thiourea. However, there is no such report yet to date for preparing Cefepime through this route. This procedure of preparing a cephalosporin compound is described in the present invention to obtain highly pure Cefepime.

DETAILED DESCRIPTION OF THE INVENTION

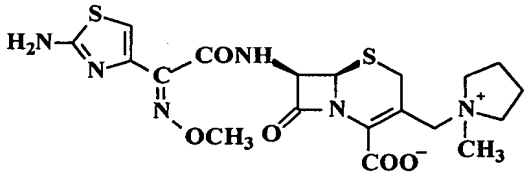
The present invention relates to 7-(4-halo-3-oxo-2-methoxyiminobutyrylamino)cephalosporin compounds of the general Formula II



Formula II

where X represents Bromine or Chlorine atom

and also to a process for preparing Cefepime of Formula I

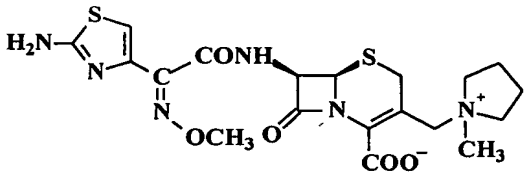


Formula I

as well as its salts and hydrates, which comprises reacting the above compounds of Formula II with thiourea,

and converting Cefepime of Formula I into a hydrate of the said salt.

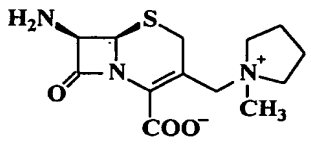
Accordingly, a process for the preparation of 7-[(Z)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetamido]-3-[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate, known as Cefepime of Formula I



Formula I

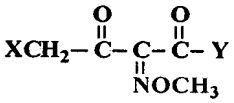
comprising the steps of

i) *N*-acylation of 7-amino-3-[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate or its salt, of Formula III, a compound prepared in a known manner,



Formula III

with halogenated carboxylic acid derivative of Formula IV, a compound prepared in a manner as herein described,

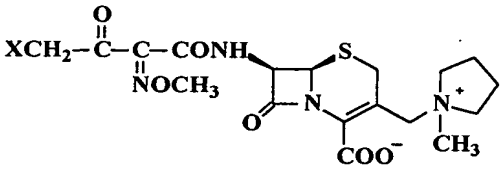


Formula IV

where X represents bromine or chlorine atom
Y represents hydroxyl or a halo group

in a suitable solvent(s), as herein described, preferably at one molar equivalent at a temperature ranging from -30°C to -10°C, to obtain a reaction mixture.

ii) adding water to the above said reaction mixture to precipitate 7-(4-halo-3-oxo-2-methoxyiminobutyrylamino)cephalosporin derivative of Formula II



Formula II

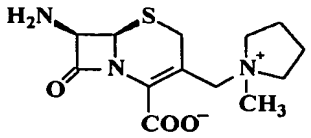
where X represents bromine or chlorine atom

iii) isolation of Formula II by filtration.

iv) reacting the said Formula II with thiourea in a solvent or a mixture of solvents such as herein described at a temperature ranging from 20°C to 40°C to obtain the desired compound, Cefepime; and

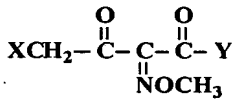
v) isolating the said Cefepime in a known manner and converting into salt form by using conventional methods.

According to the present invention, the intermediate compounds of Formula II are prepared by *N*-acylation of 7-amino-3-[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate of Formula III



Formula III

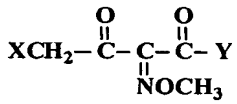
or its HX salt wherein HX is HCl, HI or H_2SO_4, with halogenated carboxylic acid of the general Formula IV



Formula IV

where X represents bromine or chlorine atom
Y represents hydroxyl or a halo group

4-(Bromo or Chloro)-2-methoxyimino-3-oxobutyric acid of Formula IV is prepared in high purity and good yield starting from *tert*-butyl acetoacetate as per the procedure described in the US Patent 5,095,149. *tert*-Butyl acetoacetate has been prepared from *tert*-butyl acetate as given in Organic Synthesis Coll. Vol. V, p-156. This is converted into the corresponding acid chloride of Formula IV



Formula IV

where X represents bromine or chlorine atom
Y represents chlorine atom

by reacting with halogenating agents such as phosphorous oxychloride, phosphorous pentachloride, oxalyl chloride etc and the acid chloride thereby produced may be isolated prior to acylation with cephalosporin compound or may be generated *in situ* and used as such. The acid chloride formation is conducted in an inert organic solvent such as chloroform, methylene chloride, acetonitrile or the like and most preferably the reaction is carried out in methylene chloride at a temperature of -25°C to -15°C.

The cephalosporin compound of Formula III and its HX salt, which is substantially free from Δ^2-isomer, may be prepared by the general procedure described in the US Patent 5,594,131.

The cephalosporin compound, 7-amino-3-[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate, which is preferably available as its hydrochloride salt, may advantageously be silylated in an inert organic solvent to form an *in situ* solution of the soluble silylated derivative. It is important to add sufficient silylating agent to solubilize the cephalosporin compound of Formula III before treating it with acid chloride of Formula V. Silylating agents which may be used are, for example, hexamethyldisilazane, trimethylchlorosilane, *N,N'*-bis(trimethylsilyl)urea, *N*-(trimethylsilyl)acetamide, *N,O*-bis(trimethylsilyl)acetamide, *tert*-butyldimethylchlorosilane or the like and most preferably *N*-(trimethylsilyl)acetamide may be used.

Suitable solvents which may be used in the acylation process are all inert organic solvents in which the silylated derivative of cephalosporin compound of Formula III is soluble, for

example, toluene, tetrahydrofuran, acetone, acetonitrile, methylene chloride, chloroform or the like and most preferably methylene chloride may be used. Soluble silylated derivative is then treated with the acid chloride of Formula V, preferably with one molar equivalent, and most preferably with a slight excess of the acid chloride. The silylation of cephalosporin compound of Formula III is completed at about 15°C to 30°C while the *N*-acylation is advantageously carried out at -30°C to -10°C.

After *N*-acylation is complete, as ascertained by the known detection methods reported in the art, water is added to the reaction mixture to precipitate 7-(4-halo-3-oxo-2-methoxyiminobutyrylamino)cephalosporin compound of the general Formula II, which is isolated by filtration. The halo intermediates of Formula II and their preparation from Cephalosporin compound of Formula III constitutes the inventive part of the present invention to prepare Cefepime.

The reaction of halo intermediates of Formula II with thiourea to prepare Cefepime, in accordance with the present invention is preferably carried out in a solvent such as ethanol, acetone, tetrahydrofuran, *N,N*-dimethylformamide, water and mixture thereof and preferably aqueous acetone is used. The reaction is generally carried out at a temperature range of 20°C to 40°C and preferably at room temperature. Thereafter, when it is desired to prepare Cefepime dihydrochloride monohydrate, the reaction mass after cyclization with thiourea is treated with sufficient amount of hydrochloric acid. The resulting reaction mixture is then diluted with water miscible appropriate solvent such as acetone to ensure the crystallization of the desired Cefepime dihydrochloride monohydrate form.

The Cefepime dihydrochloride monohydrate thus obtained is substantially free from anti-isomer and Δ^2-isomer. The present process provides control of the stereochemical configuration of methoxyimino isomer and the Δ^3-double bond of cephalosporin nucleus without the need to separate undesirable cephalosporin by-product by chromatography. Another advantage of present invention is the use of acid chloride of Formula V wherein the simple chloride ion is the leaving group and thus avoids unusual and sometimes complex leaving groups described in the art.

The examples below illustrate our invention without limiting the scope of the invention. The examples are described as two stage processes where the first stage forms the preparation of the inventive intermediates, and the second stage is their conversion to Cefepime dihydrochloride monohydrate.

Example - 1

STAGE-I:

STEP-A: SILYLATION OF 7-AMINO-3-[(1-METHYL-1-PYRROLIDINIUM)METHYL]-3-CEPHEM-4-CARBOXYLATE HYDROCHLORIDE (SOLUTION A)

To a suspension of 7-amino-3-[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate hydrochloride (10 g, 0.03 mol) in methylene chloride (100 ml) at 20-25°C, *N*-trimethylsilylacetamide solution (containing 26.72 g *N*-trimethylsilylacetamide, 0.20 mol) was added and stirred for 1 hour to obtain a clear solution. This solution was cooled to -25°C to -20°C until use.

STEP-B: PREPARATION OF 4-BROMO-2-METHOXYIMINO-3-OXOBUTYRYLCHLORIDE (SOLUTION B)

To a suspension of phosphorous pentachloride (7.5 g; 0.036 mol) in methylene chloride (62 ml), 4-bromo-2-methoxyimino-3-oxobutyric acid (7.73 g, 0.035 mol) was added in small lots over a period of 10 minutes, while maintaining the temperature between -25°C and -20°C. The reaction mass was stirred at -25°C to -20°C until the starting material's absence was noted with TLC (30 minutes). The reaction mass was then washed with water (23 ml) to remove inorganic impurities and by-products. This solution was used as such in the next step.

STEP-C: PREPARATION OF 7-(4-BROMO-2-METHOXYIMINO-3-OXOBUTYRAMIDO)-3-[(1-METHYL-1-PYRROLIDINIUM)METHYL]-3-CEPHEM-4-CARBOXYLATE (BROMO INTERMEDIATE)

Solution B was added to solution A, while maintaining the temperature between -25°C and -20°C over a period of about 10 minutes and the reaction mass was stirred for 1 hour at this temperature. Thereafter cold water (50 ml, 5°C) was added and the reaction mass was stirred at 2-5°C for 1 hour. The product thus obtained was filtered, washed with methylene chloride (20 ml) and dried to obtain the bromo intermediate as its hydrochloride salt (13.2 g). The structure of this compound was confirmed by spectroscopic data.

^{1}H NMR (300 MHz) (*DMSO-d_6*) δ	:	2.11 (*m*, 4H), 2.94 (*s*, 3H), 3.45 (*m*, 1H), 3.59 (*m*, 3H), 3.66 & 4.05 (*2d*, each 1H), 4.05 (*s*, 3H), 4.30 & 4.61 (*2d*, each 1H), 4.86 (*s*, 2H), 5.33 (*s*, 1H), 5.91 (*dd*, 1H), 9.55 (*d*, 1H).
IR (KBr) cm^{-1}	:	1785, 1714, 1678, 1610
MASS (Positive ion Mode)	:	503, 505 [M+1]; 525, 527 [M+Na] corresponding to ^{79}Br and ^{81}Br isotopes.

STAGE-II:

PREPARATION OF CEFEPIME DIHYDROCHLORIDE MONOHYDRATE

Thiourea (0.31 g, 0.0040 mol) was added to a suspension of bromo intermediate (2.0 g, 0.0037 mol, as obtained above) in a mixture of acetone (20 ml) and water (10 ml) at 20-25°C. The reaction mass was stirred at 20-25°C for 2 hours. The pH was adjusted to 6.7 using triethylamine (1 ml) and the reaction mass was stirred for 10 minutes. Thereafter, reaction mass was cooled and concentrated hydrochloric acid (2.8 ml) was added at 5-8°C followed by acetone (60 ml) The resulting slurry was cooled and stirred at 0-5°C for 1 hour. The product thus obtained was filtered, washed with acetone (2x5 ml) and dried to obtain 1.47 g of Cefepime dihydrochloride monohydrate having HPLC purity 99.42%.

^{1}H NMR (300 MHz) (*DMSO-d_6*) δ	:	2.10 (*m*, 4H), 2.94 (*s*, 3H), 3.45 (*m*, 1H), 3.59 (*m*, 3H), 3.66 & 4.04 (*2d*, each 1H), 3.93 (*s*, 3H), 4.31 & 4.61 (2*d*, each 1H), 5.33 (*d*, 1H), 5.89 (*dd*, 1H), 6.88 (*s*, 1H), 8.51 (*b*, 2H), 9.83 (*d*, 1H).
IR (KBr) cm^{-1}	:	1773, 1730, 1658, 1634
MASS (Positive ion Mode)	:	481 $[M+1]^+$; 503 $[M+Na]^+$

Example - 2

STAGE-I:

***PREPARATION OF 7-(4-CHLORO-2-METHOXYIMINO-3-OXOBUTYRAMIDO)-3-[(1-METHYL-1-PYRROLIDINIUM)METHYL]-3-CEPHEM-4-CARBOXYLATE** (CHLORO INTERMEDIATE)*

4-Chloro-2-methoxyimino-3-oxobutyric acid (6.2 g, 0.0345 mol) was added to a suspension of phosphorous pentachloride (7.5 g, 0.0360 mol) in methylene chloride (62 ml) in small lots over a period of 10 minutes while maintaining temperature between -25°C and -20°C. The reaction mass was stirred at -25°C to -20°C until completion of the reaction (~1 hour) and then washed with cold water (23 ml, 5°C). The resulting acid chloride is reacted with silyalted 7-amino-3-[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate hydrochloride as per the procedure given in Example - 1 to obtain the chloro intermediate as its hydrochloride salt. The structure of this compound was confirmed by spectroscopic data.

^{1}H NMR (300 MHz) (*DMSO-d_6*) δ	:	2.11 (*m*, 4H), 2.94 (*s*, 3H), 3.45 (*m*, 1H), 3.60 (*m*, 3H), 3.68 & 4.06 (*2d*, each 1H), 4.05 (*s*, 3H), 4.34 & 4.60 (*2d*, each 1H), 4.86 (*s*, 2H), 5.33 (*s*, 1H), 5.90 (*dd*, 1H), 9.58 (*d*, 1H)
IR (KBr) cm^{-1}	:	1785, 1717, 1682, 1609
MASS (Positive ion Mode)	:	459, 461 [M+1] corresponding to ^{35}Cl and ^{37}Cl isotopes.

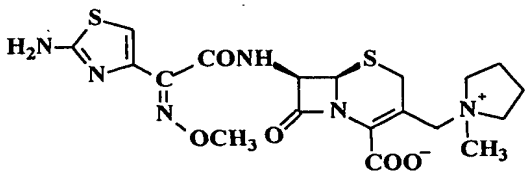
STAGE-II:

PREPARATION OF CEFEPIME DIHYDROCHLORIDE MONOHYDRATE

Thiourea (0.92 g, 0.012 mol) was added to a suspension of chloro intermediate (4.0 g, 0.008 mol, as obtained above) in a mixture of acetone (40 ml) and water (20 ml). The reaction mass was stirred at 23-30°C till completion of reaction (~6 hours). Thereafter, reaction mass was cooled and concentrated hydrochloric acid (1.2 ml) was added at 5-8°C followed by addition of acetone (92 ml). The product thus obtained was filtered, washed with acetone (2x10 ml) and dried to obtain 3.4 g of Cefepime dihydrochloride monohydrate having HPLC purity 99.19%.

WE CLAIM:

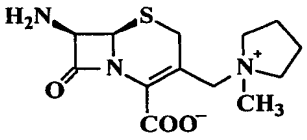
1. A process for the preparation of 7-[(Z)-2-(2-amino-4-thiazolyl)-2-(methoxyimino)acetamido]-3-[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate, known as Cefepime of Formula I



Formula I

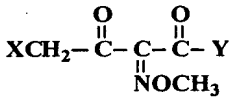
comprising the steps of

i) *N*-acylation of 7-amino-3-[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate or its salt, of Formula III,



Formula III

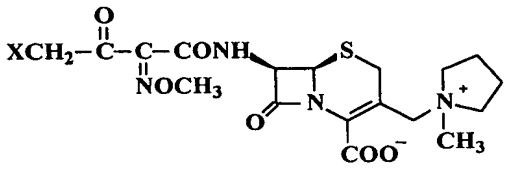
with halogenated carboxylic acid derivative of Formula IV,



Formula IV

where X represents bromine or chlorine atom
Y represents hydroxyl or a halo group

in suitable solvent(s), as herein described, preferably at one molar equivalent at a temperature ranging from -30°C to -10°C followed by addition of water to precipitate 7-(4-halo-3-oxo-2-methoxyiminobutyrylamino)cephalosporin derivative of Formula II,



Formula II

where X represents bromine or chlorine atom

ii) isolation of Formula II by filtration,

iii) reacting the said Formula II with thiourea in a solvent or a mixture of solvents such as herein described at a temperature ranging from 20°C to 40°C to obtain the desired compound, Cefepime and

iv) isolating the said Cefepime in a known manner.

2. The process as claimed in claim 1, wherein the Cephalosporin derivative of Formula III or its salt is substantially free from Δ^2-isomer.

3. The process as claimed in the preceding claims, wherein the Cephalosporin derivative of Formula III is optionally silylated in an inert organic solvent to form an *in situ* solution of the soluble silylated derivative.

4. The process as claimed in claim 3, wherein the silylating agent is selected from hexamethyldisilazane, trimethylchlorosilane, *N,N'*-bis(trimethylsilyl)urea, *N*-(trimethylsilyl)acetamide, *N,O*-bis(trimethylsilyl)acetamide, *tert*-butyldimethyl-chlorosilane or a mixture thereof.

5. The process as claimed in claim 4, the most preferable silylating agent is *N*-(trimethylsilyl)acetamide.

6. The process as claimed in Step (iv) of claim 1, wherein the solvent used is ethanol, acetone, tetrahydrofuran, *N,N*-dimethylformamide, water or a mixture thereof.

7. The process as claimed in claim 6, wherein the solvent is aqueous acetone.

8. The process as claimed in Step (iv) of claim 1, wherein the reaction is carried out at room temperature.

9. The process as claimed in claim 1, wherein the Cefepime is optionally converted into a salt form in a known manner.

10. The process as claimed in claim 9, wherein the reaction mixture after cyclization with thiourea is treated

i) with sufficient amount of an acid,
ii) diluting with water miscible appropriate solvent such as acetone to ensure the crystallization of the Cefepime salt and
iii) isolating the said salt in a known manner.

11. The process as claimed in claim 10, wherein the Cefepime salt is Cefepime dihydrochloride monohydrate.

12. The process as claimed in claims 10 and 11, wherein Cefepime dihydrochloride monohydrate is substantially free from anti isomer and Δ^2-isomer.

13. The process as claimed in any of the preceding claims, wherein stereochemical configuration of methoxyimino isomer is controlled.

14. A process for the preparation of Cefepime and or its salt is substantially, as herein described and exemplified.

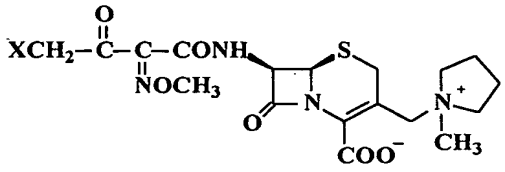
Dated this the 18th day of August 2003

AUROBINDO PHARMA LIMITED,

Dr. M. SIVAKUMARAN,
DIRECTOR.

ABSTRACT

A novel process is disclosed for the preparation of Cefepime, a cephalosporin antibiotic, using novel new intermediates of the general Formula,



where X represents Bromine or Chlorine atom

This process comprises the step of cyclizing the bromo or chloro intermediate with thiourea to produce Cefepime of high purity. A process to prepare bromo or chloro intermediate comprising the acylation of 7-Amino-3-[(1-methyl-1-pyrrolidinium)methyl]-3-cephem-4-carboxylate with 4-halo-2-methoxyimino-3-oxobutyric acid halide is also described.